## Remarks/Arguments

Applicants thank the Examiner for the Advisory Action of December 9, 2004 and for withdrawing the objection to the Specification, Priority Claim and benefit of claims 5 and 16.

Applicants also thank the Examiner for withdrawing the previous rejection of Claims 1-10, 12-17 and 19 under 35 U.S.C. §§ 102 and 103. However, the Examiner has maintained the rejection of claims 11 and 19 over Lockhart under 35 U.S.C. § 103 "because [in the Examiner's view] the passage cited on page 5, paragraphs 4-5 discusses parallel processing (a process), but does not support the instantly claimed parallel arrangement (a structural relationship)."

Applicants do not agree with these statements and rejections. Nevertheless, to expedite prosecution of the instant application, applicants have cancelled claims 11 and 19, obviating the Lockhart rejections against these claims.

The Examiner has maintained the rejection to claims 1-19 under 35 U.S.C. § 103(a) as being unpatentable over Cantor et al. (U.S. Patent No. 5,631,134, filed 5 June 1995) in view of Southern (U.S. Patent No. 5,700,637, filed 19 April 1994) and Lipshutz et al. (U.S. Patent No. 6,300,063, filed 29 November, 1995). Applicants respectfully traverse.

The Examiner admits that Cantor fails to teach or disclose

→ (a) providing at least two identical polynucleotide probe arrays . . . .

→ (b) hybridizing the target polynucleotide to said overhangs of probe polynucleotides in one array to generate a target hybridization pattern;

→ (c) hybridizing a reference polynucleotide to said overhangs of probe polynucleotides in a second array to generate a reference hybridization pattern; and

→ (d) determining the presence of a mutation in the target polynucleotide by normalizing intensity differences of hybridized probes in the reference and target hybridization patterns, comparing intensity differences of probes in the reference and target hybridization patterns and determining whether a mutation is present in the target polynucleotide.

The Examiner alleges, however, that these limitations were "routinely practiced in the art at the time the claimed invention was made," citing Southern (Column 7, lines 10-31). Southern, however, does not teach or disclose the use of two identical polynucleotide probe arrays, one of which is hybridized to target polynucleotides to generate a target hybridization pattern (element b) and the other of which is hybridized to a reference nucleotides to generate a reference hybridization pattern (element c) followed by determining the presence or absence of a mutation in the target nucleotides by normalizing intensity differences of hybridized probes (element d).

Rather, Southern teaches the opposite: providing two non-identical or different arrays using the same nucleotide solution. While the passage at Col. 7, lns. 10-31 is short of experimental details, it is specifically stated that "A technique for doing this [5.4 Analyzing Several Sequences Simultaneously] is described in Example 3 below." Col. 7, lns. 15-16.

Example 3 is explicitly teaches using non-identical arrays: "For further study of the effects of shorter sequences on hybridization behavior, we constructed two arrays; one (a) of 24 oligonucleotides and the other (b) of 72 oligonucleotides. (Emphasis added). The example goes on in detail to describe hybridization of the same nucleotide solution to each of the two non-identical oligonucleotides. Thus, there is no teaching of hybridizing a target and reference sequence. Thus, Southern in no way makes up for the deficiencies of Cantor. Indeed, Southern teaches away from the instant invention: contrary to the requirements of the instant claims, Southern teaches the use of two non-identical arrays and hybridization of the same nucleotide solution to each.

The Examiner states that Southern teaches the use of a second array, but fails to note that Southern's second array is entirely different than Southern's first array: "Southern teaches a similar method for determining the presence of a mutation in a target polynucleotide comprising hybridizing a target polynucleotide to array [sic] and a reference polynucleotide to a second array . . . and determining the presence of a mutation by comparing a reference and target hybridization patterns . . . ." Final Office Action of 8/17/2004, pp 12-13.

There is nothing remotely similar about Southern's hybridization to "a second array" to Applicants claimed hybridization of two distinct nucleotide solutions (target and reference) to two "identical polynucleotide probe arrays." In Example 3, "a technique for doing" section 5.4 Analyzing Several Sequences Simulataneously, Col. 7, lns. 10-31, relied on heavily by the Examiner, two distinctly different arrays are constructed, see Tables 1(a) and 1(b), one of 24 oligonucleotides and the other of 72 oligonucleotides. Southern, Col. 10, lns. 15-18. Each array was then hybridized with the identical nucleotide sequence: a single $^{32}P$ labeled 19-mer oligonucleotide sequence, 5' CTCCTGAGGAGAAGTCTGC 3'. The slides were then subjected to autoradiography followed by elution at various temperatures and washing, followed again by autoradiography. Thus, four critical limitations of the claimed invention (see b to d above) are entirely missing from Southern.

The Examiner also states that Southern can discriminate between single mismatch sequences using for example the techniques in Example 3: "the hybridization conditions are extremely stringen conditions to discriminate between single mismatch sequences as taught by Southern (Column 10, line 57-67-column 11, page 4) for the expected benefits of identifying mutations accurately, efficiently and economically . . . ." Final Office Action at p. 13. However, Southern's own data reveals that his techniques cannot reliably distinquish between single g\base pair mis-matches. Referring to the 24 mer oligonucleotide, the perfectly matached 21 mer sequence give a substantial lower melting point, and hence is less stable, than a mismatch sequence:

The perfectly matched sequence GAG GAC TCC TCT TCA GAC melted off at 60°C. (Table I). Whereas the single base pair mismatch AG GAC TCC TCT TCA GAG G melted at a higher temperature 66°C. Clearly, the perfectly matched duplex should have given a higher melting point than the less perfectly matched duplex. This is the essence of allowing mutation detection. However, Southern fails to show this most basic property and the Southern system is not reliably capable of detecting mutations. Moreover, Southern's system teaches an entirely different detection system: non-identical arrays arrays probed with the samc solution as that required by the instant invention.
4.

Cantor and Southern teach or suggest nothing about the final step of claim 1 of the instant invention: (d) determining the presence of a mutation in the target polynucleotide by (i) normalizing intensity differences of hybridized probes in the reference and target hybridization patterns, (ii) comparing intensity differences of probes in the reference and target hybridization patterns and (iii) determining whether a mutation is present in the target polynucleotide.

In an attempt to remedy this deficiency, the Examiner cites Lipshutz, stating that Lipshutz et al. "teach a similar method comprising hybridizing target polynucleotides to probes having an overhang (Column 5, line 21-24) on an array comprising perfect match and mismatch probes (Example 2 [sic], Column 12, lines 21-24) wherein normalization intensity differences comprises dividing the perfect match hybridization intensity by the hybridization intensity for mismatch probe (citing Lipshutz at Column 9, lines 36-Column 10, lines 56). The Examiner contends that "[i]t would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the normalization of Lipschutz et al to the mutation detection of Cantor et al and Southern to thereby easily and accurartely identify mutations as taught by Lipshutz et al (Column 9, line 36-Col. 10, ln. 56)." Final Office Action of 8/17/2004 at p. 16.

As discussed extensively above, Southern fails to teach or disclose essential elements of the claimed invention. The claimed invention requires providing two identical probe arrays, hybridizing a first such array to target nucleotides to provide a target hybridization pattern and references sequences to a second probe to provide a reference sequence, followed by normalizing hybridization intensities followed by comparing hybridization patterns to determine the presence or absence of a mutation.

There is no teaching or suggestion what ever in Lipshcutz of providing identical arrays followed by hybridization with different oligonucleotide solution to generate different patterns. Lipschutz specifically teaches the use of a single array:

> "In particular, each sample from each of the individuals studied is amplified and hybridized to a P246 chip. The 246 chip employs a poly-tiling scheme and contains marker-specific control probes covering regions upstream and downstream from the single-base polymorphism. The

> significance of the control probes is that given that the target sample is amplified, these probes will display both perfect matches (PM) and single-base mismatches (MM) at known mismatch positions regardless of the target genotype. Even though in this document our description of the genotype calling method is based on the intensity data of a specific offset block (7/20, 10/20, 13/20) and a specific strand (T7, T3), this method is easily generalizable to accommodate data combining multiple offset blocks and strands.. As the elements of claim 1, are not taught or disclosed in any of the prior art cited by the Examiner, applicants respectfully request that the objections to claim 1 be withdrawn."

This single chip method taught by Lipschutz is entirely different and operates by different principals and controls than that of the instant invention. Thus, Lipshutz does not in any way make up for the deficiencies of Southern.

The Examiner also points to textual references in the Lipshutz patent concerning normalizing data and picking perfectly matched from mismatched sequences. Final Office Action of August 17, 2004 at p. 13. The Examiner appears to be referring to teachings in Lipschutz approximating element D of the instantly claimed invention. But, irrespective of that teaching the absence in Cantor, Souther and Lipschutz of providing two identical arrays for hybridization to different nucleotide solutions renders the Examiner's non-patentability claim fatal.

Moreover, the claims are directed to detecting mutations whereas, Lipshutz is directed at determining whether polymorphic markers in DNA are heterozygote, homozygote, homozygote with a first polymorphic market, or homozygote with a second polymorphic marker. There is no teaching or suggestion that the techniques of Lipschutz could be used in the context of the instant invention.

Claim 2 is also patentable. Cantor mentions ligating the hybridized polynucleotide to the probe, but as described in detail above, the other elements of claim 1 (elements (a) – (d)), on which claim 2 depends (35 U.S.C. § 112), are not taught or disclosed by Cantor or any other reference cited by the Examiner. Applicants respectfully request that the objections to claim 2 be withdrawn.

Claim 3 is also patentable. Again, Cantor mentions ligating the hybridized polynucleotide to the probe, but as described in detail above, the other elements of claim 1 (elements (a) – (d)), on which claim 3 depends, are not taught or disclosed by Cantor or any other reference cited by the Examiner. Applicants respectfully request that the objections to claim 3 be withdrawn.

Claim 4 is drawn to the method of claim 1, wherein the overhangs have free 5'-ends. Claim 5 is drawn to the method of claim 1, wherein the overhangs have free 3'-ends. Claim 6 is drawn to the method of claim 1, wherein the n-mer comprises from about 4 to about 50 nucleotides. The Examiner points out facets of Cantor teaching these features. But, importantly, elements a-d of claim 1 on which claims 4-6 depend are not taught or disclosed by Cantor or any other reference cited by the Examiner. Hence, claims 4-6 are patentable and applicants respectfully request that the objections to these claims be withdrawn.

Claim 7 is drawn to a method of claim 1, wherein the mutation is a substitution mutation. Claim 8 is drawn to the method of claim 1, wherein the mutation is a deletion mutation. Claim 9 is drawn to a method of claim 1, wherein the mutation is an insertion mutation. The Examiner contends that each of these would have been obvious to one of ordinary skill in the art. However, claims 7-9 incorporate all the elements of claim 1, including a-d, which the Examiner's references do not teach or disclose. Hence, claims 7-9 are patentable and applicants respectfully request that these objections be withdrawn.

Claim 10 is drawn to the method of claim 1, in which said target polynucleotide is selected from the group consisting of: a cystic fibrosis transmembrane conductance regulator gene, a p53 gene, a mitochondrial DNA, or an HIV gene. Again, the Examiner admits that none of these is taught in Cantor. Instead, the Examiner alleges without support that such mutations would have been known to one of skill in the art. Applicants disagree with this proposition. Moreover, claim 10's patentability turns not only on whether the particular mutations would have been known to one of skill in the art, but on whether elements a-d would have been obvious to one of skill in the art. As discussed at length above, the Examiner's references wholly fail to prove this. Thus, claim 10 is

patentable over the prior art and applicants respectfully request that the objections to this claim be withdrawn.

To expedite prosecution, Claim 11 has been cancelled, obviating the Examiner's quizzical rejection, rejecting an dependent claim as obvious but allowing the corresponding dependent claim as non-obvious over the same rejection.

With respect to claim 12, the Examiner reiterates the rejections made to claim 1 involving Cantor in combination with Southern and Lipschutz. For the sake of brevity, applicants refer the Examiner to the full-length discussion of these references, supra. To summarize, in contrast to the claimed invention, Southern teaches using two non-identical arrays and hybridizing them to the same nucledotide solution. Lipshutz in no way addresses the failures of Cantor and Sourthern addressed above. Moreover, Lipschutz teaches the detection of polymorphisims, not mutations as required by the claims of the instant invention.

Claim 13 depends from claim 12 and further limits it to the polynucleotide being ligated to the probe. Notwithstanding that there is some teaching about this feature in Cantor, claim 12 is non-obvious for the reasons set forth above with regard to claim 2 due to the inadequacy of Southern and Lipshutz. Because claim 12 is patentable over Cantor in view of Southern and Lipshutz, claim 13 is patentable and non-obvious under basic tenants of claim construction, irrespective of the additional teaching in Cantor regarding ligation to the probe.

Claim 14 is directed to the method of claim 12, wherein in step c), the hybridized second target polynucleotide is ligated to the probe. As pointed out above substantial limitations of the independent claims are not taught or disclosed by Cantor, Southern and Lipschutz. Hence, despite the Examiner's statements about hybridization probes, claim 14 would not have been obvious to one of skill in the art.

Claims 15 (overhangs have free 5' ends), 16 (overhangs have free 3' ends) and 17 (n-mer comprises from about 4 to 50 nucleotides are patentable for the reasons set forth above: there is no teaching or disclosure of providing two identical arrays, hybridizing one array with target nucleotides to form a target hybridization pattern and hybridizing

the other with reference oligonucleotides to form a reference pattern followed by normalizing intensity differences and comparing intensity differences to determine the absence or presence of a mutation.

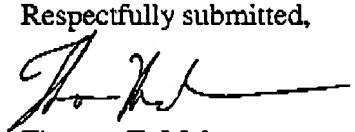
In summary, the Examiner's finding of obviousness of the instant invention over Cantor in view of Southern is due to a misapprehension of the teachings of Southern. Southern teaches using different or non-identical arrays hybridized to the same nucleotide sample. There is simply no basis in Southern for concluding that the instant invention is obvious. Lipschutz also teaches a different method of using arrays than the presently claim invention: Lipschutz teaches using a single arrays. Moreover, Lipschutz is directed to detecting polymorphisms of various types, not mutations as claimed by the instant invention. Applicants respectfully request that the rejections based on these interpretations be withdrawn (which includes all the pending rejections to claims to pending claims 1-10 and 12-17).

Applicants believe the application is now in condition for allowance and should be passed to issue. If the Examiner feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at (408) 731-5875.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account 01-0431.

If the Examiner has any questions pertaining to this application, the Examiner is requested to contact the undersigned attorney.

Respectfully submitted,



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